

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Thomas Cremers, et al.	Confirmation No. 5528
Application No.: 10/596,348	Group Art Unit: 1614
Filed: July 14, 2006	Examiner: Rao, Savitha
For: THE COMBINATION OF A SEROTONIN REUPTAKE INHIBITOR AND A HISTAMINE H3 RECEPTOR ANTAGONIST, INVERSE AGONIST OR PARTIAL AGONIST	

Date: August 10, 2009

DECLARATION OF CONNIE SÁNCHEZ MORILLO, D. SC.,
PURSUANT TO 37 C.F.R. §1.132

Sir:

I, Connie Sánchez Morillo, D. Sc., hereby declare as follows:

1. I am an expert in the field of the present invention as evidenced by my Curriculum Vitae, attached as Exhibit A.
2. I have reviewed the subject patent application which discloses the combination administration of a serotonin reuptake inhibitor and a histamine H3 receptor antagonist, inverse agonist or partial agonist. I have also reviewed the Office Action issued February 20, 2009, and present claims 1, 5-21, and 35-36, in connection with the subject patent application.
3. The subject application discloses that co-administration of a high-affinity H3 receptor antagonist and a serotonin reuptake inhibitor produces a significant increase in the level of serotonin in terminal areas (of the brain), as compared to the administration of the serotonin reuptake inhibitor alone. See page 19, lines 1-4 of the subject application as filed. The subject application discloses that the administration of H3 antagonist alone causes no increase in serotonin levels. The subject application further discloses that serotonin (5-HT) levels were measured in microdialysis experiments. See page 28, line 5 through page 30, line 15 of the subject application as filed.
4. As disclosed in the subject application, the combination of a H3 receptor antagonist and a serotonin reuptake inhibitor elicits an unexpected synergistic effect on the central nervous

system (CNS). It was not obvious at the time of filing the subject application that the combination of a H3 receptor antagonist and a serotonin reuptake inhibitor would be synergistic.

5. In support of my statement made in the preceding paragraphs three and four, I submit the following:
- (a) Experiments were conducted in the laboratories of University of Groningen to assess the effects of co-administration of thioperamide or ciproxifan, both high-affinity H3 receptor antagonists, and citalopram, a serotonin reuptake inhibitor. Extracellular levels of 5-HT were measured in the ventral hippocampus of rats following:
 - (i) subcutaneous (s.c.) administration of citalopram (10 $\mu\text{mol/kg}$),
 - (ii) subcutaneous (s.c.) administration of thioperamide (12.25 $\mu\text{mol/kg}$ ¹),
 - (iii) co-administration of citalopram (10 $\mu\text{mol/kg}$ s.c.) plus thioperamide (12.25 $\mu\text{mol/kg}$ s.c.),
 - (iv.) subcutaneous (s.c.) administration of ciproxifan (15 mg/kg),
 - (v.) co-administration of citalopram (10 $\mu\text{mol/kg}$ s.c.) plus ciproxifan (15 mg/kg s.c.), and
 - (vi.) co-administration of citalopram (10 $\mu\text{mol/kg}$ s.c.) plus ciproxifan (1 mg/kg s.c.).
 - (b) Elevated 5-HT levels were measured in dialysates by microdialysis at each 15-minute interval following administration (injection = time zero). Microdialysis techniques are well-known in the art.
 - (c) The level of 5-HT in each dialysate was compared and plotted over a period of 150 minutes. See the figures attached hereto as Exhibits B and C.

¹ 12.25 $\mu\text{mol/kg}$ = 5 mg/kg based on molecular weight (MW) of thioperamide (Sigma-Aldrich Catalog #T123, CAS # 148440-81-7, MW = 408).

6. In the experiments as represented in the attached figure (Exhibit B), administration of thioperamide alone (12.25 $\mu\text{mol/kg}$; -▲- Exhibit B) demonstrated baseline levels of 5-HT. 100% of baseline levels means that no increase or decrease was observed above the normal baseline levels of 5-HT in the hippocampus of the rat, such normal baseline levels being observed prior to administration of any drug (see -▲- Exhibit B). In these experiments, administration of citalopram alone (10 $\mu\text{mol/kg}$; -■-) demonstrated an increase over baseline to nearly 500% of baseline 5-HT levels within 45 minutes and steadying to these levels for 150 minutes. These experiments further demonstrated that co-administration of citalopram (10 $\mu\text{mol/kg}$ s.c.) plus thioperamide (12.25 $\mu\text{mol/kg}$) elicited a significantly greater increase, e.g. approximately 900% of baseline 5-HT levels, at time intervals of 75, 90, 105, and 150 minutes following injection (see -●- Exhibit B, and page 30, lines 1-6 of the specification).
7. Since thioperamide alone fails to elicit 5-HT levels above baseline, then the additive effect of the co-administration of citalopram plus thioperamide on 5-HT levels is expected to be the same as citalopram alone, or 5-HT levels approximately 500% of baseline. The co-administration of citalopram plus thioperamide, however, consistently elicited a much greater increase over baseline 5-HT levels, e.g. 900% of baseline, when compared to the effect of citalopram alone. This greater increase in 5-HT levels induced by co-administration citalopram and thioperamide is evidence of an unexpected synergistic effect.
8. Similarly, co-administration of citalopram (10 $\mu\text{mol/kg}$ s.c.) plus ciproxifan (15 mg/kg) elicited a significantly greater increase, e.g. over 1000% of baseline 5-HT levels, at time intervals of 60, 75, 90, 105, 120 and 135 minutes following injection (see -▼- Exhibit C, and page 30, lines 10-15 of the specification).
9. Given the prior art teachings, one would not conclude that H3 antagonists, inverse agonists or partial agonists, and serotonin reuptake inhibitors produce a synergistic effect, let alone an additive effect, on serotonin levels in the brain. There is no prior art evidence of increased serotonin levels as induced by H3 receptor antagonism or inhibition.
10. It is generally known and accepted in the art that inducing an elevation of serotonin levels

in the brain leads to more efficacious antidepressants. By administering H3 receptor antagonists, inverse agonists or partial agonists in combination with a serotonin reuptake inhibitor, these H3 receptor inhibitors may be used to augment the effect of the serotonin reuptake inhibitor by causing such further increase of 5-HT levels. Through this synergistic effect, H3 antagonists, inverse agonists or partial agonists provide significant improvement to the therapeutic effect (efficacy) of a serotonin reuptake inhibitor like citalopram.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statements may jeopardize the validity of the application or any patent issued thereon.

08/10/09

Date

Connie Sánchez Morillo

Connie Sánchez Morillo, D. Sc.

CURRICULUM VITAE

Connie Sánchez (Morillo)

Current responsibilities:

Vice President, Neuroscience, Lundbeck Research, USA, Inc.

Previous responsibilities (H.Lundbeck A/S):

- 2001-2004.** Manager of the escitalopram (Ciprallex®) pharmacology research team, team task to investigate in depth the mechanism of action of escitalopram.
- 1999-2001.** Head of department of neuropharmacology, which is responsible for in vivo epilepsy research and sleep research.
- 1997-1999.** Head of in vivo screening department, which was responsible for in vivo screening models of anxiety, depression and psychosis.
- 1995-1997.** Research manager for drug discovery projects within depression and anxiety.
- 1986-1995.** Scientist and senior scientist in Pharmacological Research Departments and responsible for establishment of animal models of anxiety and depression
- 1981-1986.** Clinical Research Department as research fellow and project manager

Other employment:

- 1980-1981.** Practising histology (methods, techniques and diagnostics) at Càtedra de Histologia, Facultat de Medicina, University of Barcelona, Spain.
- 1978-1980.** Flavour chemist analysing and composing food flavours at Grindsted Products A/S, Brabrand, Denmark.

University degrees:

M Sc & D Sc. Pharmacology

Scientific societies, working groups and other academic activities:

Member, previous board member and secretary of Danish Society of Pharmacology and Toxicology. Member of Danish Society of Neuroscience, European Behavioural Pharmacology Society, Scandinavian Society of Psychopharmacology, International Society of Psycho-Neuro-Endocrinology, and Society of Neuroscience.

Member of various working groups designing post graduated courses (statistics, pharmacology and physiology at basic and advanced levels) for laboratory personnel.

Ph D and M Sc students. Approved as external examiner at the University of Copenhagen. Lecturing at postgraduate courses at the Pharmaceutical and Veterinarian and Agricultural Universities.

Referee for European Journal of Pharmacology, Neuropsychopharmacology, Neuropharmacology, Pharmacology Biochemistry and Behaviour, Pharmacology and Toxicology, Psychopharmacology, Behavioural Brain Research, Brain Research, Physiology and Behaviour, European Journal of Neuroscience, Journal of Neural Transmission, Journal of European Neuropsychopharmacology.

Publications:

More than 80 publications in peer reviewed journal, more than 200 abstracts and poster presentations, more than 100 oral presentations at symposia and several use patents.

Patent Publications:

1. US Patent No. 6,262,061, issued July 17, 2001, entitled "Treatment of panic attacks"
2. US Patent No. 6,358,966, issued March 19, 2002, entitled "Treatment of depression"
3. PCT International Application Publication No. WO2002/102387, published on December 27, 2002, entitled "Treatment of neuropathic pain"
4. US Patent Application Publication No. US20040029957 A1, published February 12, 2004 entitled "Treatment of Neurotic Disorders"
5. US Patent Application Publication No. US20040029958 A1, published February 12, 2004 entitled "Treatment of Neurotic Disorders"
6. US Patent Application Publication No. US20040192764A1, published September 30, 2004 entitled "Use of enantiomeric pure escitalopram"
7. US Patent Application Publication No. US20040192765A1, published September 30, 2004 entitled "Use of enantiomeric pure escitalopram"
8. US Patent Application Publication No. US20040192766A1, published September 30, 2004 entitled "Use of enantiomeric pure escitalopram"
9. US Patent Application Publication No. US20040198809A1, published October 7, 2004 entitled "Use of enantiomeric pure escitalopram"
10. US Patent Application Publication No. US20040198810A1, published October 7, 2004 entitled "Use of enantiomeric pure escitalopram"
11. US Patent Application Publication No. US20040198811A1, published October 7, 2004 entitled "Use of enantiomeric pure escitalopram"
12. US Patent Application Publication No. US20050234093A1, published October 20, 2005 entitled "Gaboxadol for treating depression and other affective disorders"
13. US Patent No. 6,960,613, issued November 1, 2005, entitled "Treatment of neurotic disorders"
14. US Patent Application Publication No. US20050288371A1, published December 29, 2005 entitled "Treatment of neuropathic pain, fibromyalgia or rheumatoid arthritis"
15. US Patent Application Publication No. US20070117844A1, published May 24, 2007 entitled "5-HTP Combination Therapy"
16. US Patent Application Publication No. US20070123584A1, published May 31, 2007 entitled "A method of treating premenstrual dysphoric disorder with escitalopram"
17. US Patent No. 7,265,151, issued September 4, 2007, entitled "Treatment of neurotic disorders"

18. US Patent No. 7,271,194, issued September 18, 2007, entitled "Treatment of neurotic disorders"
19. US Patent Application Publication No. US20070213370A1, published September 13, 2007 entitled "5-HTP Combination Therapy"
20. US Patent Application Publication No. US20070276035A1, published November 29, 2007 entitled "Treatment of neurotic disorders"
21. US Patent Application Publication No. US20080004338A1, published January 3, 2008

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3. Hyttel J, Arnt J, Bøgesø KP, Christensen AV, Larsen J-J, Lembøl HL, Meier E and Sánchez C (1988). Neurochemical and behavioural profile of Lu 17-133, (+)-trans-4-[3-(3,4-dichlorophenyl)-indan-1-yl]-1-piperazine ethanol, an inhibitor of the uptake of dopamine and noradrenaline. *Drug Dev. Res.* 13, 213-230.
4. Sánchez C (1989). The effects of dopamine D₁ and D₂ receptor agonists on body temperature in male mice. *Eur. J. Pharmacol.* 171, 201-206.
5. Sánchez C, Arnt J, Dragsted N, Hyttel J, Lembøl HL, Meier E, Perregaard J, and Skarsfeldt T (1991). Neurochemical and in vivo pharmacological profile of sertindole, a limbic-selective neuroleptic compound. *Drug Devel. Res.* 22, 239-250.
6. Arnt J, Hyttel J and Sánchez C (1992). Partial and full dopamine D₁ receptor agonists in mice and rats: relation between behavioural effects and stimulation of adenylate cyclase activity in vitro. *Eur. J. Pharmacol.* 213, 259 - .
7. Arnt J, Sánchez C and Skarsfeldt T (1992). Relevance of drug discrimination methods for the evaluation of antipsychotic drugs. *Eur. Neuropsychopharmacol.* 2, 223-224.
8. Hyttel J, Arnt J, Costall B, Dragsted N, Lembøl HL, Meier E, Naylor RJ, Nowak G, Sánchez C and Skarsfeldt T (1992). *Clin. Neuropharmacol.* 15, suppl. 1, 267-268.
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10. Perregaard J, Arnt J, Bøgesø K and Sánchez C (1992). Non-cataleptogenic centrally acting dopamine D₂ and serotonin 5-HT₂ antagonists within a series of 3-substituted 1-(4-fluorophenyl)-1H-indoles. *J. Med. Chem.* 35, 1092-1101.
11. Perregaard J, Andersen K, Hyttel J and Sánchez C (1992). Selective centrally acting serotonin 5-HT₂ antagonists. Part I: 2- and 6- substituted 1-phenyl-3-(4-piperidinyl)-1H-indoles. 35, 4813-4822.
12. Sánchez C and Arnt J (1992). Effects on body temperature in mice differentiates between dopamine D₂ receptor agonists with high and low efficacies. *Eur. J. Pharmacol.* 211, 9-14.
13. Perregaard J, Sánchez C and Arnt J (1993). Recent development in anxiolytics. *Cur. Opin. Ther. Pat.* 1, 101-128.
14. Sánchez C (1993). Effect of serotonergic drugs on footshock-induced ultrasonic vocalization. *Behav. Pharmacol.* 4, 269-277.

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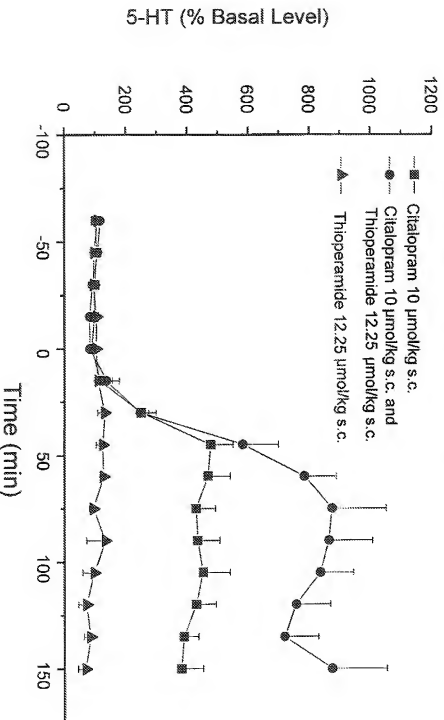
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Citalopram + thioperamide



Citalopram + ciproxifan

